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Congenital Vocal Cord Paralysis With Possible Autosomal Recessive Inheritance: Case Report and Review of the Literature

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We describe an infant with congenital vocal cord paralysis born to consanguineous parents. While autosomal dominant and X-linked inheritance have been previously reported in this condition, we conclude that the degree of parental consanguinity in this case strongly suggests autosomal recessive inheritance. Although we cannot exclude X-linked inheritance, evidence from animal studies demonstrates autosomal recessive inheritance and provides a possible molecular basis for congenital vocal cord paralysis.

KEY WORDS: vocal cord paralysis, autosomal recessive, vagus

INTRODUCTION

Vocal cord paralysis is a common cause of neonatal stridor [Grundfast and Harley, 1989]. However, familial vocal cord dysfunction is rare; the known familial cases suggest a genetic cause. Hereditary vocal cord paralysis described to date has followed either autosomal dominant or X-linked recessive patterns of inheritance, and the age of onset of symptoms is variable. We describe two affected brothers born to consanguineous parents. Although this pedigree may represent X-linked vocal cord paralysis [Plott, 1964], the possibility of autosomal recessive inheritance must be considered in light of the parental consanguinity.

CLINICAL REPORT

A.S. is a male infant born to a 31-year-old G4P2102 mother at 39 weeks of gestation. The pregnancy was uneventful and progressed to an uncomplicated spontaneous vaginal delivery. From the moment of birth, the baby was noted to be stridorous and cyanotic. Laryngoscopy showed bilateral congenital vocal cord paralysis (CVCP) and an immediate improvement in the clinical condition was noted following intubation with a number 3.5 endotracheal tube.

Physical examination showed a male infant with a birth weight of 3,140 g (25th percentile), head circumference (OFC) of 35.5 cm (75th percentile), and length 53 cm (80th percentile). The infant was slightly hypotonic, irritable, and demonstrated a poor sucking reflex, but intact gag, Moro, and grasp reflexes. Apart from a high arched palate, the physical findings were unremarkable.

Laryngoscopy on day 4 of life showed bilateral vocal cord immobility without adduction or abduction. The subglottis, trachea, and carina were all normal. MRI of the brain and brain stem was normal and echocardiography demonstrated normal cardiac anatomy. Tracheostomy was performed on day 11. A cine-esophagogram demonstrated ineffective swallowing with aspiration of contrast. Therefore, a gastrostomy tube was inserted on day 25. The child began to sit at 6 months; at 1 year, he began to walk and to take oral feeds but did not show any signs of recovering vocal cord function.

The parents are double first cousins. The maternal grandparents are first cousins and the paternal grandparents are related, probably as second or third cousins (Fig. 1). Neither parent has any obvious speech abnormality or swallowing difficulty. Laryngoscopy of the parents was recommended but declined. The couple's 7-year-old son has CVCP and tracheomalacia. He presented with severe stridor at birth and required a tracheostomy. The tracheostomy has remained in place and the child has not shown signs of recovering vocal cord function. He has also required gastrostomy tube feeds because of swallowing incoordination. Several hypoglycemic seizures occured at 2 years of age due to complications related to the gastrostomy feedings. Although his neurodevelopmental milestones had been delayed by approximately 10 months, the older male sibling is now a good student in the second grade of a

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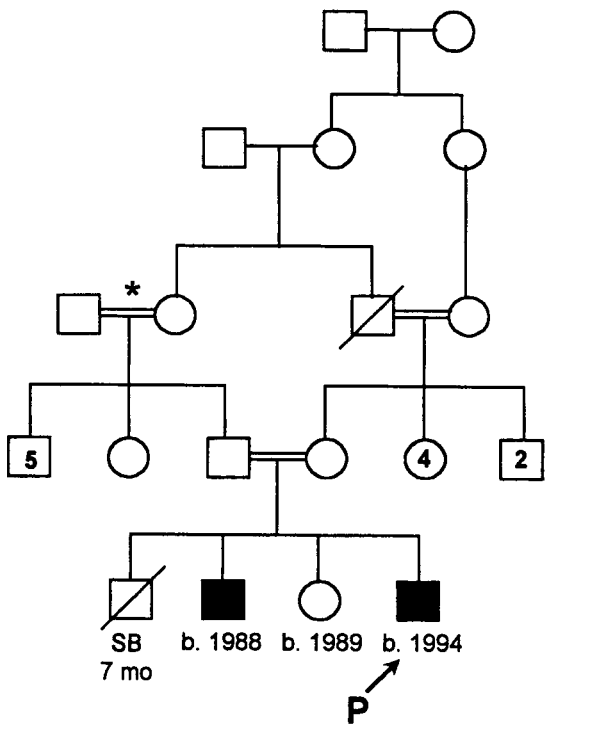

Fig. 1. Pedigree demonstrating consanguinity.

regular school. The parents have had a stillborn male fetus at 7 months of gestation. The couple's 5-year-old daughter is in good health.

DISCUSSION

A review failed to document any reports of pedigrees demonstrating autosomal recessive inheritance. Only one previously reported case of familial vocal cord paralysis involved consanguineous parents and they were related distantly [Schinzel, 1990]. In addition, on laryngoscopy the mother was found to have unilateral laryngeal abductor paralysis. Therefore, the inheritance in that family was most likely autosomal dominant with variable expression. For the family that we have described, the degree of consanguinity of the paternal grandparents is unknown, although the father reported that they are not first cousins. Based on the known consanguinity in this family, the inbreeeding coefficient for the two affected brothers is calculated to be $1/16 + 1/64$ which equals $5/64$ or 0.078. Since the paternal grandparents are also consanguineous, the degree of relatedness between the two brothers is actually slightly higher.

Several other families have been reported with autosomal dominantly inherited congenital vocal cord paralysis. Gacek [1976] described a father and two sons with abductor vocal cord paralysis who were all treated with a tracheostomy. Mace [1978] reported ten affected individuals in a five generation pedigree who had congenital bilateral adductor paralysis with many instances of male-to-male transmission. Morelli et al. [1982] reported a family with seven affected individuals in three generations and Grundfast and Milmoe [1982] found congenital hereditary bilateral abductor vocal cord paralysis in a father and his son and daughter. The authors suspected an abnormality in the vicinity of the brainstem nuclei of the vagus nerve as the cause. Cunningham et al. [1985] described a brother and two sisters in one family who presented with neonatal stridor. Vocal cord dysfunction was confirmed in two of the children by endoscopic examination. Pulmonary function tests suggested defective chemical regulation of breathing, which depends on neural transmission from the carotid body through the nucleus ambiguus to the posterior cricoarytenoid muscles. Isaacson and Moya [1987] reported on a mother who required a tracheotomy on the second day of life for CVCP. She remained tracheotomized for approximately one year and follow-up laryngoscopy at age 24 years demonstrated good adduction bilaterally, but only partial abduction. Her daughter also presented with CVCP and required tracheotomy soon after birth. The vertical transmission of this trait with no other affected relatives in the pedigree suggests a new mutation with autosomal dominant inheritance.

Rare cases of familial vocal cord paralysis associated with other anomalies have been reported. Tucker [1983] described a man and his daughter who were born with bilateral ptosis of the eyelids and bilateral recurrent laryngeal nerve paralysis. Hawkins [1990] reported familial vocal cord dysfunction associated with digital anomalies. Holinger [1979] described an association between Charcot-Marie-Tooth disease (hereditary motor and sensory neuropathy) and familial vocal cord paralysis in a mother and her son.

Plott [1964] and Watters and Fitch [1973] reported laryngeal abductor paralysis in two different families which occurred only in males and was consistent with X-linked recessive inheritance. The boys also presented with mental deficiency. Plott speculated about dysgenesis of the nucleus ambiguus as a cause.

Recent advances in the molecular biology of embryonic development and morphogenesis enable us to speculate about a possible inherited basis for this condition. Homeobox, or *Hox* genes, encode DNA-binding proteins and are thought to specify cell identity along the anteroposterior axis of the embryo [Chisaka et al., 1992]. This family of genes consists of 38 members organized in man and mouse into 4 linkage groups on 4 different chromosomes. The expression of *Hox* genes is stage- and region-specific and misexpression or inactivation of *Hox* genes results in characteristic morphological defects. Chisaka et al. [1992] performed gene targeting in mouse embryo-derived stem cells to disrupt homeobox gene *Hox-1.6*. The homozygous littermates demonstrated defects in the hindbrain and associated cranial nerves and ganglia. Particularly prominent was the severe reduction or absence of connections between the glossopharyngeal and vagus nerves and their brainstem ganglia. Moreover, these nerves were displaced rostrally along the anteroposterior axis. The mice that were heterozygous at the *Hox-1.6* locus were normal. In

similar experiments, Swiatek and Gridley [1993] performed gene targeting experiments in mice to delete *Krox20* genes, zinc finger coding genes expressed during vertebrate hindbrain development. The homozygous mutant animals died shortly after birth and were found to have fusion of the superior ganglia of the glossopharyngeal and vagus nerves resulting in a disorganization of the nerve roots of these ganglia as they entered the brain stem. Again, the heterozygotes were normal. Involvement of these genes in CVCP would suggest autosomal recessive inheritance.

Although X-linked inheritance, autosomal dominant transmission of a mutated gene with incomplete penetrance, or germinal mosaicism remain possibilities in this family, autosomal recessive inheritance is strongly suggested by the degree of parental consanguinity. Evidence from animal studies provides additional support for a possible recessive mode of inheritance.

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